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ORIGINAL ARTICLE

Liver function declines with increased age

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Abstract

Introduction: Age itself is not considered a contraindication for high impact surgery. However, the aging process of the liver remains largely unknown. This study evaluates age-dependent changes in liver function using a quantitative liver function test.

Methods: Between January 2005 and December 2014, 508 patients underwent ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS) for the assessment of liver function. These included 203 patients with healthy livers (group A) and 57 patients with HCC and Child-Pugh A (group B). ^{99m}Tc-mebrofenin-uptake-rate of the whole liver corrected for body surface area (cMUR) was calculated for all patients. Linear regression analysis was performed to assess the relationship between age and cMUR.

Results: The mean cMUR was 8.50 ± 2.05%/min/m^2 and 6.94 ± 2.03%/min/m^2 in group A and B, respectively. A negative linear correlation was found between patient's age and cMUR in group A, r = 0.244, p = 0.000. In group B, there was no correlation between age and cMUR, however, a trend in decline of liver function with age was noted.

Conclusion: This study shows that liver function deteriorates with age. Since the regenerative capacity of the liver correlates with liver function, this finding should be taken into account when assessing surgical risk in patients considered for major liver resection.

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Introduction

In 2012, life expectancy in the Netherlands was 79.1 years for men and 82.8 years for women while the remaining life expectancy for elderly at the age of 65 was +18.3 years for men and +21.2 years for women.[1] This corresponds with an increase in life expectancy of 12.6% for males and 14.1% for females in the time period 1950–2012.[1] In accordance with this trend, along with expanded possibilities for liver resection, we observe increasing rates of liver resections performed in the elderly. During the last 5 years in our department, approximately 16% of major liver resections were undertaken in patients of ≥75 years old. This percentage increases to nearly 30% when the elderly are defined as patients aged 70 years or older, which is in line with rates reported in literature.[2] The described trend underscores the importance of risk assessment associated with major liver resection (≥3 liver segments) in the elderly.

From the oncological point of view, the older could equally benefit from surgical treatment as the younger patients since comparable (disease-free) survival rates are described in patients with colorectal liver metastases (CRLM) and hepatocellular carcinoma (HCC).[2–5] Controversy, however, exists regarding postoperative morbidity and/or mortality in the older patient. Recent studies report that the elderly tolerate liver resection as well as younger patients[6–9] while at the same time, a significantly higher risk of postoperative morbidity and mortality after major liver resections has been reported in the elderly.[2,10] These outcomes often are explained by the increased incidence of comorbidities among aged patients, leading to higher peri- and postoperative risks.

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Despite these contradictory reports, it is largely accepted that age itself should not be considered a contraindication provided that a strict preoperative protocol is followed for selection of patients eligible for major liver resection. As with all high impact surgery, screening for comorbidities and evaluation of patient's condition should be undertaken during preoperative work-up. In addition, disease-specific predictors for unfavorable post-operative outcome, e.g. tumor diameter, number and location of lesions, should also be weighed against future remnant liver (FRL) volume and function in the light of the individual risk of postoperative liver failure.

Postoperative liver failure is one of the most severe complications after major liver surgery[11] and irrespective of tumor entity, is strongly associated with the extent of resection and underlying parenchymal disease. The occurrence of post-operative liver failure is mainly dictated by the functional capacity of the FRL.[12] Accurate preoperative, quantitative assessment of liver function is therefore crucial to prevent this complication by modulating the FRL (Portal vein embolization, ALPPS).[13] Increased rates of postoperative liver failure in aged patients after liver surgery have been reported.[14] However, the aging process of the human liver and its functional consequences remain largely unknown.

^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS) with SPECT-CT enables quantitative assessment of hepatic uptake function. HBS allows at the same time independent evaluation of total liver function and segmental liver function, i.e. the FRL-function,[13] in both patients with diseased or normal liver parenchyma. This functional test has been used for preoperative selection of patients in the setting of major liver surgery and for monitoring of the hypertrophy response after preoperative portal vein embolization (PVE) or ALPPS.[12,15,16]

Apart from measuring base-line liver function, we hypothesize that a quantitative liver function test such as HBS, also indicates the regenerative capacity of the liver, in other words, when age influences the function of the liver, it will also influence the regenerative capacity of the liver remnant after resection. Knowledge of such age-dependent changes of the functional capacity of the liver therefore contributes to accurate preoperative risk assessment in a continuously aging patient population requiring major liver resections. The aim of this study was to evaluate age-dependent changes in total liver function in both patients with normal and affected liver parenchyma.

Methods

Patients

All adult patients with presumed healthy liver parenchyma (group A) or patients with pre-cirrhotic liver parenchyma (group B) who underwent ^{99m}Tc-mebrofenin hepatobiliary scintigraphy (HBS) between January 2005 and December 2014 for the assessment of hepatic uptake function were included. Patients diagnosed with hepatic metastases irrespective of origin, or benign tumors were considered to have healthy liver parenchyma. Patients with hepatocellular carcinoma (HCC) and who were classified as Child-Pugh A were considered as pre-cirrhotic.

Patients who were cholestatic or could have been cholestatic prior to HBS were excluded as hyperbilirubinemia may affect HBS results. For this reason, all patients diagnosed with perihilar cholangiocarcinoma or intrahepatic cholangiocarcinoma were excluded. Furthermore, all patients with parenchymal diseases other than those classified as Child-Pugh A were excluded.

Assessment of liver function using HBS

HBS was performed after 4 h fast to standardize the measurements. Patients were positioned supine on the imaging table of a large-field-of-view (FOV) SPECT/CT camera (Symbia T16; Siemens) positioned over the liver and heart region. After intravenous administration of 200 MBq freshly prepared ^{99m}Tc-mebrofenin (Bridatec; GE-Amersham Health), dynamic acquisition was obtained (36 frames of 10 s/frame, 128 matrix), which was used for calculation of the hepatic mebrofenin uptake rate (MUR). Data were processed on a Hermes workstation (Hermes Medical Solutions, Sweden).

The following parameters were studied: MUR and MUR corrected for body surface area (cMUR).[17–19] For the calculation of body surface area the formula by Mosteller and colleagues was used. MUR is expressed as %/min while cMUR is expressed as %/min/m^2.

Data collection

Patient characteristics were collected form the digital patient records. Diagnosis and status of the liver parenchyma were extracted from the histology reports. cMUR was extracted from nuclear medicine reports.

Study endpoints

The primary endpoint of this study was age-dependent changes in total cMUR defined as correlation between cMUR and age.

The secondary endpoint of this study was differences in the age-dependent changes in total cMUR between patients with presumed healthy liver parenchyma, i.e. group A, and pre-cirrhotic patients, i.e. group B.

Statistical analysis

Statistical analysis was performed with Statistical Package of Social Sciences (SPSS 22.0, IBM Inc., Armonk (NY) USA). Normally distributed continuous data are expressed as mean ± standard deviation (SD), while non-normally distributed data are presented as median along with interquartile range (IQR). Correlation between age and cMUR was studied using linear regression. Continuous data were compared using independent T test or One-way ANOVA test. All statistical tests were two tailed and differences were considered significant at a p-value of <0.05.

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